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(12) **EUROPEAN PATENT APPLICATION**

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(54) **Protein rab3 GEP**

(57) The present invention provides a protein Rab3 GEP which is a GDP/GTP exchange protein active on the Rab3 subfamily small G proteins, which has an amino acid sequence of Sequence ID No. 1 or an amino acid sequence substantially the same as that of the Sequence ID No. 1, a cDNA sequence coding this protein, and genomic DNA sequence to which the cDNA sequence or a part thereof hybridizes. According to the invention, there is provided a novel protein (Rab3 GEP) specific for the Rab3 subfamily small G proteins which are involved in intercellular vesicle trafficking, and a genetic material for industrial utilization thereof. This protein is useful, not only for clarification of the molecular mechanism of intracellular vesicle trafficking which is an important cellular event, but also for development of diagnosis, prevention and therapy of neural diseases and the like.

**Description****Field of the Invention**

5 The present invention relates to a GDP/GTP exchange protein (GEP) specific for the Rab3 subfamily small GTP-binding proteins (G proteins). More particularly, the present invention relates to the protein Rab3 GEP useful for clarification of a molecular mechanism of intracellular vesicle trafficking essential for maintenance of homeostasis of a living organism, or for diagnosis or development of preventive and therapeutic drugs for neural diseases.

**10 Description of the Related Art**

In a general cell composing a living organism, there exist a number of organelles surrounded by unit membranes, such as endoplasmic reticulum, Golgi complex, lysosome, and endosome, and material transport between these organelles is accomplished by accurate trafficking of vesicles (intracellular vesicle trafficking). For instance, membrane  
15 receptors, such as EGF and PDGF receptors, are synthesized on ribosomes and transported to the endoplasmic reticulum membrane from where they are transported to the plasma membrane through the Golgi complex by vesicles. Soluble substances, such as those secreted outside the cell from the plasma membrane, are also transported by vesicles. For instance, hormones and digestive enzymes are synthesized on ribosomes and transported to the endoplasmic reticulum lumen from where they are transported to the plasma membrane. Exocytosis, endocytosis, and transcytosis  
20 are performed by intracellular vesicle trafficking. There are two exocytotic pathways: one is a regulated pathway and the other is a constitutive pathway. In the former pathway, in most cases exocytosis is regulated by  $Ca^{2+}$ . Intracellular vesicle trafficking is also involved in various other cell functions, such as formation of cell polarity, cytokinesis and cell motility. Although intracellular vesicle trafficking is one of the very important cellular events as described above, the molecular mechanism has not as yet been completely clarified. The mechanism of intracellular trafficking clarified so far is as follows.

There are at least four principal mechanisms in intracellular vesicle trafficking: (i) budding of the vesicle from the donor membrane; (ii) targetting of the vesicle to the acceptor membrane; (iii) docking of the vesicle to the acceptor membrane; (iv) fusion of the vesicle with the acceptor membrane. The vesicle trafficking is regulated by the Rab family small G proteins. There are approximately thirty members in the Rab family and each member is located in each mem-  
30 brane compartment and exerts its specific function. The mode of action of the Rab family members in the targetting and docking processes in intracellular vesicle trafficking is as follows: the GDP-bound inactive form of each Rab family member is complexed with Rab GDP dissociation inhibitor (GDI) and remains in the cytoplasm. When it is released from Rab GDI, GEP exerts its action, and the Rab family member is converted to the GTP-bound active form. This GTP-bound form binds to its specific target protein on the vesicle, which is consequently transported to the acceptor mem-  
35 brane. Before or after fusion of the vesicle with the membrane, the GTP-bound form is converted to the GDP-bound form. Once the GDP-bound form is produced on the membrane, it is complexed with Rab GDI and translocated from the membrane to the cytoplasm.

On the other hand, the present inventors have discovered Rab3A as a member of the Rab family small G proteins (J. Biol. Chem., 263:2879-2904, 1998), and revealed that Rab3A plays an important role in  $Ca^{2+}$ -dependent exocytosis,  
40 particularly in neurotransmitter release (Int. Rev. Cytol., 133: 187-230, 1992). They have further found Rab GDI, a regulatory protein of Rab3A (J. Boil. Chem., 265: 2333-2337, 1990) and Rabphilin3A, a target protein of Rab3A (Mol. Cell. Biol., 13: 2061-2068, 1993).

In intracellular vesicle trafficking, as described above, the mode of action of the Rab family members has been clarified, and the research efforts made by the present inventors have permitted specification of regulatory proteins and tar-  
45 get proteins of the Rab family members.

However, in order to understand the more detailed mechanism of intracellular vesicle trafficking, it is indispensable to find GEP and GAP specific for each Rab family member or Rab subfamily. At least, no GEP or GAP specific for the Rab3 subfamily members (Rab3A, -B, -C and -D) has not as yet been identified. Two GEPs for Rab3A, Mss4 (Nature,  
50 361: 464-467, 1993) and Rab3A GRF (J. Boil. Chem., 267: 22715-22718, 1992) have been so far found: the former is not specific for the Rab3 subfamily, and the latter has been just partially purified and its primary structure has not been reported.

**Summary of The Invention**

55 The present invention has an object to provide a novel protein (Rab3 GEP) specific for the Rab3 subfamily small G proteins involved in intracellular vesicle trafficking, in a state that the structure (amino acid sequence) and properties thereof have not been clarified.

Another object of the invention is to provide a material for genetic engineering manipulation of this Rab3 GEP.

The invention provides a protein Rab3 GEP, which is a GDP/GTP exchange protein specific for the Rab3 subfamily small G proteins, and comprises the amino acid sequence of Sequence ID No. 1.

Further, the invention provides an animal protein having substantially the same amino acid sequence as that of the Sequence ID No. 1.

5 In addition, the invention provides a cDNA sequence encoding the amino acid sequence of the Sequence ID No. 1 or an amino acid sequence substantially the same as that of the Sequence ID No. 1.

The invention also provides a genomic DNA sequence to which the cDNA set forth above or a part thereof is hybridized.

10 According to the invention, there is provided a novel protein (Rab3 GEP) specific for the Rab3 subfamily small G proteins involved in intracellular vesicle trafficking, and a genetic material for industrially utilizing such a protein. This protein is useful not only for clarifying the molecular mechanism of intracellular vesicle trafficking which is an important cellular event, but also for developing diagnosis, prevention and therapy of neural diseases.

### Brief Description of The Drawings

15 Fig. 1 illustrates the column chromatographies: (A) shows Superdex 200 column chromatography, and (B) shows the second hydroxyapatite column chromatography (O represents the  $[^3\text{H}]\text{GDP}$  bound which is an indicator of Rab3 GEP activity, ---, absorbance at 280 nm, and the lower panels illustrate SDS-polyacrylamide gel electrophoresis (PAGE) analysis with silver staining);

20 Fig. 2 illustrates the substrate specificity of Rab3 GEP II (A-1, B-1) and Mss4 (A-2, B-2): (A-1, A-2) Rab3A (O), Rab2 ( $\Delta$ ), Rab5A (O), Rab10 ( $\Delta$ ) and Rab11 ( $\square$ ); and (B-1, B-2) Rab3A (O), Rab3B ( $\Delta$ ), Rab3C ( $\Delta$ ), Rab3D (O); and

Fig. 3A illustrates the requirement of Rab3 GEP II (A-1) and Mss4 (A-2) for lipid modifications of Rab3A, representing their activity to lipid-modified Rab3A (O) and lipid-unmodified Rab3A (O); and Fig. 3B illustrates the sensitivity of Rab3 GEP II and Mss4 to Rab GDI (with Rab3 GEP II (O), with Mss4 ( $\Delta$ ), without Rab3 GEP II or Mss4 (O))

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### Detailed Description of The Invention

A protein Rab3 GEP of the invention is purified from rat brain synaptic soluble fraction through successive column chromatographies by using lipid-modified Rab3A as a substrate, and has a molecular weight of about 200 kD as estimated by SDS-PAGE (about 270 kD as estimated by gel filtration). A cDNA clone was obtained from a rat cDNA library with partial amino acid sequences of this purified protein as probes, and the cDNA amino acid sequence was analyzed. This protein Rab3 GEP was confirmed to have the amino acid sequence of Sequence ID No. 1.

30 Therefore, Rab3 GEP of the invention is available by inserting the foregoing cDNA into an appropriate expression vector, and expressing the cDNA in *Escherichia coli* and the like. A protein derived from other animals than rat can be obtained by a process, for example, of isolating a cDNA from the cDNA library of the animal by using the cDNA of the invention or a part thereof as a probe, and causing expression in a suitable host-vector system. The thus obtained protein derived from an animal other than rat also has an amino acid sequence substantially the same as that of Sequence ID No. 1.

40 The cDNA sequence of the invention includes, as described above, cDNA of rat or cDNA coming from any animal other than rat. The genomic DNA sequence of the invention include DNA sequence of any of all the animal species.

### Examples

45 A protein Rab3 GEP of the invention will be described further in detail by means of Examples. The invention is not however limited by the following examples.

#### Example 1: Purification of Rab3 GEP

50 Synaptic soluble fraction was prepared from 80 rat brains. A half of the fraction (500 ml, 455 mg of protein) was adjusted to 0.2 M NaCl and applied to a Q-Sepharose FF column (2.6 x 10 cm) equilibrated with Buffer A (20 mM Tris/Cl at pH 7.5 and 1 mM DTT) containing 0.2 M NaCl. Elution was performed with 350 ml of Buffer A containing 0.5 M NaCl. Fractions of 10 ml each were collected. When the Rab3 GEP activity was assayed by measuring the dissociation of  $[^3\text{H}]\text{GDP}$  from lipid-modified Rab3A, the activity was observed in Fractions 5-19.

55 These fractions (150 ml, 159 mg of protein) were collected, and NaCl was added to give a final concentration of 2 M. The sample was applied to a phenyl-Sepharose column (2.6 x 10 cm) equilibrated with Buffer A containing 2 M NaCl. Elution was performed with a 360-ml linear gradient of NaCl (2-0 M) in Buffer A, followed by 180 ml of Buffer A. Fractions of 6 ml each were collected. The Rab3 GEP activity was observed in Fractions 52-63.

## Sequence Listing

Sequence ID No.:1

5 Length:1602 amino acids

Type: protein

Sequence

10 Met Val Gln Lys Lys Phe Cys Pro Arg Leu Leu Asp Tyr Leu Val Ile  
1 5 10 15  
15 Val Gly Ala Arg His Pro Ser Ser Asp Ser Val Ala Gln Thr Pro Glu  
20 25 30  
Leu Leu Arg Arg Tyr Pro Leu Glu Asp His Pro Glu Phe Pro Leu Pro  
35 40 45  
20 Pro Asp Val Val Phe Phe Cys Gln Pro Glu Gly Cys Leu Ser Val Arg  
50 55 60  
25 Gln Arg Arg Met Ser Leu Arg Asp Asp Thr Ser Phe Val Phe Thr Leu  
65 70 75 80  
Thr Asp Lys Asp Thr Gly Val Thr Arg Tyr Gly Ile Cys Val Asn Phe  
30 85 90 95  
Tyr Arg Ser Phe Gln Lys Arg Met Pro Lys Glu Lys Ala Glu Gly Gly  
100 105 110  
35 Ala Gly Pro Arg Gly Lys Glu Gly Ala His Ala Pro Cys Ala Ser Glu  
115 120 125  
Glu Ala Ala Thr Glu Ser Ser Glu Ser Gly Ser Thr Leu Gln Pro Pro  
40 130 135 140  
Ser Ala Asp Ser Thr Pro Asp Val Asn Gln Ser Pro Arg Gly Lys Arg  
145 150 155 160  
45 Arg Ala Lys Ala Gly Asn Arg Ser Arg Asn Ser Thr Leu Thr Ser Leu  
165 170 175  
Cys Val Leu Ser His Tyr Pro Phe Phe Ser Thr Phe Arg Glu Cys Leu  
50 180 185 190  
Tyr Thr Leu Lys Arg Leu Val Asp Cys Cys Ser Glu Arg Leu Leu Gly

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	195	200	205
	Lys Lys Pro Gly Ile Pro Arg Gly Val Gln Arg Asp Thr Met Trp Arg		
5	210	215	220
	Ile Phe Thr Gly Ser Leu Leu Val Glu Glu Lys Ser Ser Ala Leu Leu		
	225	230	235
10	240		
	His Asp Leu Arg Glu Ile Glu Ala Trp Ile Tyr Arg Leu Leu Arg Ser		
	245	250	255
	Pro Val Pro Val Ser Gly Gln Lys Arg Val Asp Ile Glu Val Leu Pro		
15	260	265	270
	Gln Glu Val Gln Gln Ala Leu Thr Phe Ala Leu Pro Asp Pro Ser Arg		
	275	280	285
20	290		
	Phe Thr Leu Val Asp Phe Pro Leu His Leu Pro Leu Glu Leu Leu Gly		
	295	300	
	Val Asp Ala Cys Leu Gln Val Leu Thr Cys Ile Leu Leu Glu His Lys		
25	305	310	315
	320		
	Val Val Leu Gln Ser Arg Asp Tyr Asn Ala Leu Ser Met Ser Val Met		
	325	330	335
30			
	Ala Phe Val Ala Met Ile Tyr Pro Leu Glu Tyr Met Phe Pro Val Ile		
	340	345	350
	Pro Leu Leu Pro Thr Cys Met Ala Ser Ala Glu Gln Leu Leu Leu Ala		
35	355	360	365
	Pro Thr Pro Tyr Ile Ile Gly Val Pro Ala Ser Phe Phe Leu Tyr Lys		
40	370	375	380
	Leu Asp Phe Lys Met Pro Asp Asp Val Trp Leu Val Asp Leu Asp Ser		
	385	390	395
	400		
45	Asn Arg Val Ile Ala Pro Thr Asn Ala Glu Val Leu Pro Ile Leu Pro		
	405	410	415
	Glu Pro Glu Ser Leu Glu Leu Lys Lys His Leu Lys Gln Ala Leu Ala		
50	420	425	430
	Ser Met Ser Leu Asn Thr Gln Pro Ile Leu Asn Leu Glu Lys Phe His		

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	435	440	445
	Glu Gly Gln Glu Thr Pro Leu Leu Gly Arg Phe Ser Asn Asp Leu		
5	450	455	460
	Gln Ser Thr Pro Ser Thr Glu Phe Asn Pro Leu Ile Tyr Gly Asn Asp		
	465	470	475 480
10	Val Asp Ser Val Asp Val Ala Thr Arg Val Ala Met Val Arg Phe Phe		
	485	490	495
	Asn Ser Ala Asn Val Leu Gln Gly Phe Gln Met His Thr Arg Thr Leu		
15	500	505	510
	Arg Leu Phe Pro Arg Pro Val Val Ala Phe Gln Ala Gly Ser Phe Leu		
	515	520	525
20	Ala Ser Arg Pro Arg Gln Thr Pro Phe Ala Glu Lys Leu Ala Arg Thr		
	530	535	540
	Gln Ala Val Glu Tyr Phe Gly Glu Trp Ile Leu Asn Pro Ser Asn Tyr		
25	545	550	555 560
	Ala Phe Gln Arg Ile His Asn Asn Thr Phe Asp Pro Ala Leu Ile Gly		
	565	570	575
30	Asp Lys Pro Lys Trp Tyr Ala His Gln Leu Gln Pro Ile His Tyr Arg		
	580	585	590
35	Val Tyr Asp Ser Asn Ser Gln Leu Ala Glu Ala Leu Ser Val Pro Pro		
	595	600	605
	Glu Arg Asp Ser Glu Ser Asp Pro Thr Asp Asp Ser Gly Ser Asp Ser		
40	610	615	620
	Met Asp Tyr Asp Asp Ser Ser Ser Ser Tyr Ser Ser Leu Gly Asp Phe		
	625	630	635 640
45	Val Ser Glu Met Met Lys Cys Asp Ile Asn Gly Asp Thr Pro Asn Val		
	645	650	655
	Asp Pro Leu Thr His Ala Ala Leu Gly Asp Ala Ser Glu Val Glu Ile		
50	660	665	670
	Asp Glu Leu Gln Pro Gln Lys Glu Gly Glu Glu Pro Gly Pro Asp Ser		

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	675	680	685
	Glu Asn Ser Gln Glu Asn Leu Pro Leu Arg Ser Ser Ser Ser Thr Thr		
5	690	695	700
	Ala Ser Ser Ser Pro Ser Thr Ile Val His Gly Ala His Ser Glu Pro		
	705	710	715
10	Ala Asp Ser Thr Glu Val Gly Asp Lys Ala Ala Thr Gly Ile Ser Lys		
	725	730	735
	Pro Leu Pro Pro Val Pro Pro Ser Ile Cys Lys Ser Thr Val Asp Arg		
15	740	745	750
	Arg Gln Thr Glu Thr Gly Glu Gly Ser Val Cys Gln Arg Thr Tyr Asp		
	755	760	765
20	His Pro Tyr Phe Glu Pro Gln Tyr Gly Ser Pro Ala Glu Glu Asp Asp		
	770	775	780
	Asp Glu Gln Gly Glu Ser Tyr Thr Pro Arg Phe Ser Gln His Ala Ser		
25	785	790	795
	Gly Ser Arg Ala Gln Lys Leu Leu Arg Pro Asn Ser Leu Lys Leu Ala		
30	805	810	815
	Ser Asp Ser Asp Ala Glu Ser Asp Ser Arg Ala Ser Ser Pro Asn Ser		
	820	825	830
35	Thr Val Ser Asn Asn Ser Thr Glu Gly Phe Gly Gly Ile Met Ser Phe		
	835	840	845
	Ala Ser Ser Leu Tyr Arg Asn His Ser Thr Ser Phe Ser Leu Ser Asn		
40	850	855	860
	Leu Thr Leu Pro Thr Lys Gly Ala Arg Glu Lys Thr Thr Pro Phe Pro		
	865	870	875
45	Ser Leu Lys Gly Asn Arg Arg Ala Leu Val Asp Gln Lys Ser Ser Val		
	885	890	895
	Ile Lys His Ser Pro Thr Val Lys Arg Glu Pro Pro Ser Pro Gln Gly		
50	900	905	910
	Arg Ser Ser Asn Ser Ser Glu Asn Gln Gln Phe Leu Lys Glu Val Val		

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	915	920	925
5	His Ser Val Leu Asp Gly Gln Gly Val Gly Trp Leu Asn Met Lys Lys		
	930	935	940
	Val Arg Arg Leu Leu Glu Ser Glu Gln Leu Arg Val Phe Val Leu Ser		
10	945	950	955
	Lys Leu Ser Arg Ala Val Gln Ser Glu Asp Asp Ala Arg Gln Asp Val		
	965	970	975
15	Ile Gln Asp Val Glu Ile Ser Arg Lys Val Tyr Lys Gly Met Leu Asp		
	980	985	990
	Leu Leu Lys Cys Thr Val Leu Ser Leu Glu Gln Ser Tyr Ala His Ala		
20	995	1000	1005
	Gly Leu Gly Gly Met Ala Ser Ile Phe Gly Leu Leu Glu Ile Ala Gln		
	1010	1015	1020
25	Thr His Tyr Tyr Ser Lys Glu Pro Asp Lys Arg Lys Arg Ser Pro Thr		
	1025	1030	1035
	Glu Asn Val Asn Thr Pro Val Gly Lys Asp Pro Gly Leu Ala Gly Arg		
30	1045	1050	1055
	Gly Asp Pro Lys Ala Met Ala Gln Leu Arg Val Pro Gln Leu Gly Pro		
	1060	1065	1070
35	Arg Ala Pro Ser Ala Thr Gly Arg Gly Pro Lys Glu Leu Asp Thr Arg		
	1075	1080	1085
	Ser Leu Lys Glu Glu Asn Phe Val Ala Ser Val Gly Pro Glu Val Ile		
40	1090	1095	1100
	Lys Pro Val Phe Asp Leu Gly Glu Thr Glu Glu Lys Lys Ser Gln Ile		
45	1105	1110	1115
	Ser Ala Asp Ser Gly Val Ser Leu Ala Ser Ala Ser Gln Arg Thr Asp		
	1125	1130	1135
	Gln Asp Ser Val Ile Gly Val Ser Pro Ala Val Met Ile Arg Ser Ser		
50	1140	1145	1150
	Ser Gln Asp Ser Glu Val Ser Asn Ser Ser Gly Glu Thr Leu Gly Ala		

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	1155	1160	1165
5	Asp Ser Asp Leu Ser Ser Asn Ala Gly Asp Gly Pro Gly Gly Glu Gly		
	1170	1175	1180
	Ser Ala His Leu Ala Ser Ser Arg Ala Thr Leu Ser Asp Ser Glu Ile		
10	1185	1190	1195
	Glu Thr Asn Ser Ala Thr Ser Thr Ile Phe Gly Lys Ala His Ser Leu		
	1205	1210	1215
15	Lys Pro Lys Glu Lys Pro Ala Ser Ser Pro Val Arg Ser Ser Glu Asp		
	1220	1225	1230
	Val Ser Gln Arg Val Tyr Leu Tyr Glu Gly Leu Leu Gly Arg Asp Lys		
20	1235	1240	1245
	Gly Ser Met Trp Asp Gln Leu Glu Asp Ala Ala Met Glu Thr Phe Ser		
	1250	1255	1260
25	Ile Ser Lys Glu Arg Ser Thr Leu Trp Asp Gln Met Gln Phe Trp Glu		
	1265	1270	1275
	Asp Ala Phe Leu Asp Ala Val Met Leu Glu Arg Glu Gly Met Gly Met		
30	1285	1290	1295
	Asp Gln Gly Pro Gln Glu Met Ile Asp Arg Tyr Leu Ser Leu Gly Glu		
	1300	1305	1310
35	His Asp Arg Lys Arg Leu Glu Asp Asp Glu Asp Arg Leu Leu Ala Thr		
	1315	1320	1325
	Leu Leu His Asn Leu Ile Ser Tyr Met Leu Leu Met Lys Val Asn Lys		
40	1330	1335	1340
	Asn Asp Ile Arg Lys Lys Val Arg Arg Leu Met Gly Lys Ser His Val		
	1345	1350	1355
45	Gly Leu Val Tyr Ser Gln Gln Ile Asn Glu Val Leu Asp Gln Leu Thr		
	1365	1370	1375
	Asn Leu Asn Gly Arg Asp Leu Ser Ile Arg Ser Ser Gly Ser Arg His		
50	1380	1385	1390
	Met Lys Lys Gln Thr Phe Val Val His Ala Gly Thr Asp Thr Asn Gly		

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	1395	1400	1405
5	Asp Ile Phe Phe Met Glu Val Cys Asp Asp Cys Val Val Leu Arg Ser		
	1410	1415	1420
	Asn Ile Gly Thr Val Tyr Glu Arg Trp Trp Tyr Glu Lys Leu Ile Asn		
10	1425	1430	1435
	Met Thr Tyr Cys Pro Lys Thr Lys Val Leu Cys Leu Trp Arg Arg Asn		1440
	1445	1450	1455
15	Gly Ser Glu Thr Gln Leu Asn Lys Phe Tyr Thr Lys Lys Cys Arg Glu		
	1460	1465	1470
	Leu Tyr Tyr Cys Val Lys Asp Ser Met Glu Arg Ala Ala Ala Arg Gln		
20	1475	1480	1485
	Gln Ser Ile Lys Pro Gly Pro Glu Leu Gly Gly Glu Phe Pro Val Gln		
	1490	1495	1500
25	Asp Met Lys Thr Gly Glu Gly Gly Leu Leu Gln Val Thr Leu Glu Gly		
	1505	1510	1515
	Ile Asn Leu Lys Phe Met His Asn Gln Val Phe Ile Glu Leu Asn His		1520
30	1525	1530	1535
	Ile Lys Lys Cys Asn Thr Val Arg Gly Val Phe Val Leu Glu Glu Phe		
	1540	1545	1550
35	Val Pro Glu Ile Lys Glu Val Val Ser His Lys Tyr Lys Thr Pro Met		
	1555	1560	1565
	Ala His Glu Ile Cys Tyr Ser Val Leu Cys Leu Phe Ser Tyr Val Ala		
40	1570	1575	1580
	Ala Val Arg Ser Ser Glu Glu Asp Leu Arg Thr Pro Pro Arg Pro Val		
	1585	1590	1595
45	Ser Ser		1600

50 Claims

1. A protein Rab3 GEP, which is a GDP/GTP exchange protein specific for the Rab3 subfamily G proteins, and comprises the amino acid sequence of Sequence ID No. 1.
- 55 2. An animal protein having substantially the same amino acid sequence as that of the Sequence ID No. 1.
3. A cDNA sequence coding the amino acid sequence of the Sequence ID No. 1 or an amino acid sequence substantially the same as that of the Sequence ID No. 1.

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4. A genomic DNA sequence to which the cDNA sequence of claim 3 or a part thereof is hybridized.

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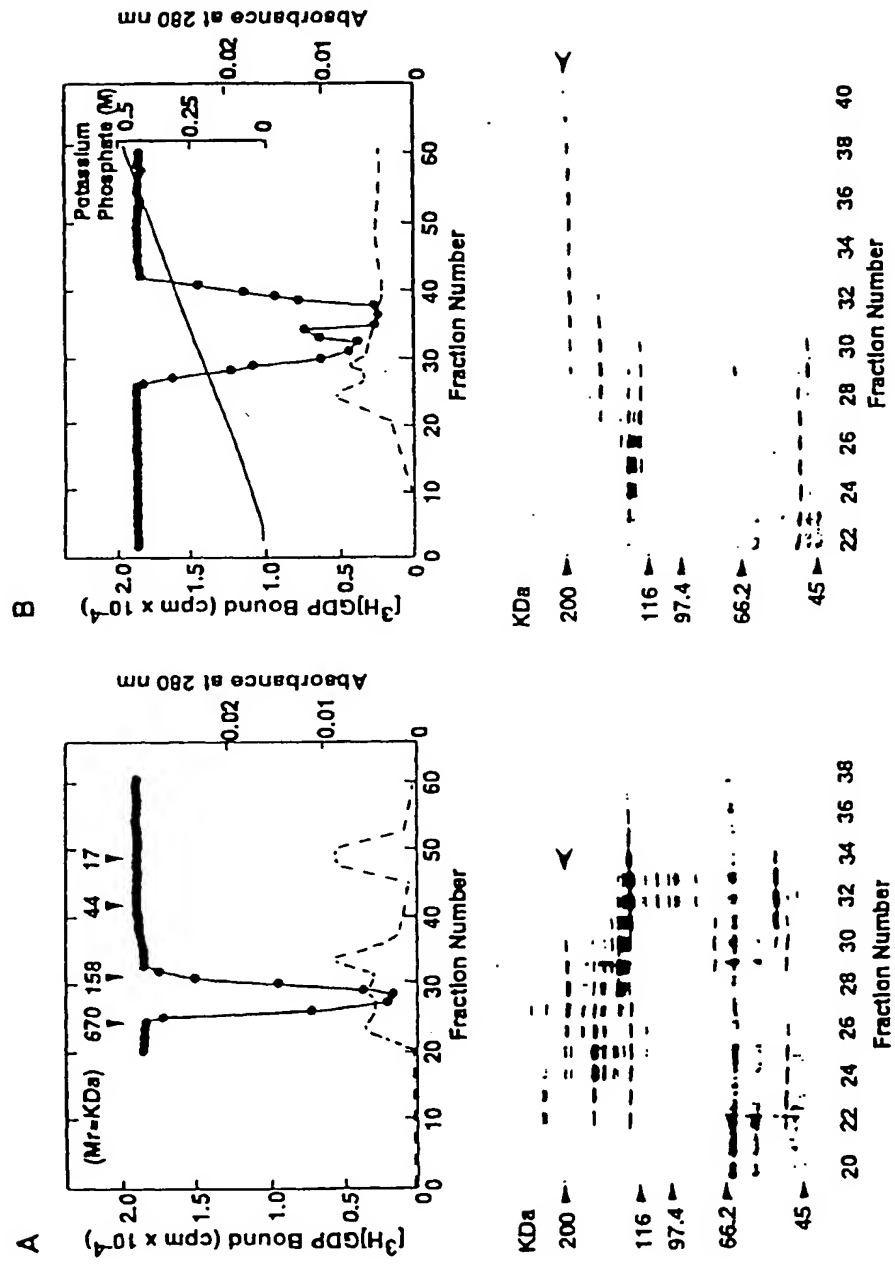
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Fig. 1



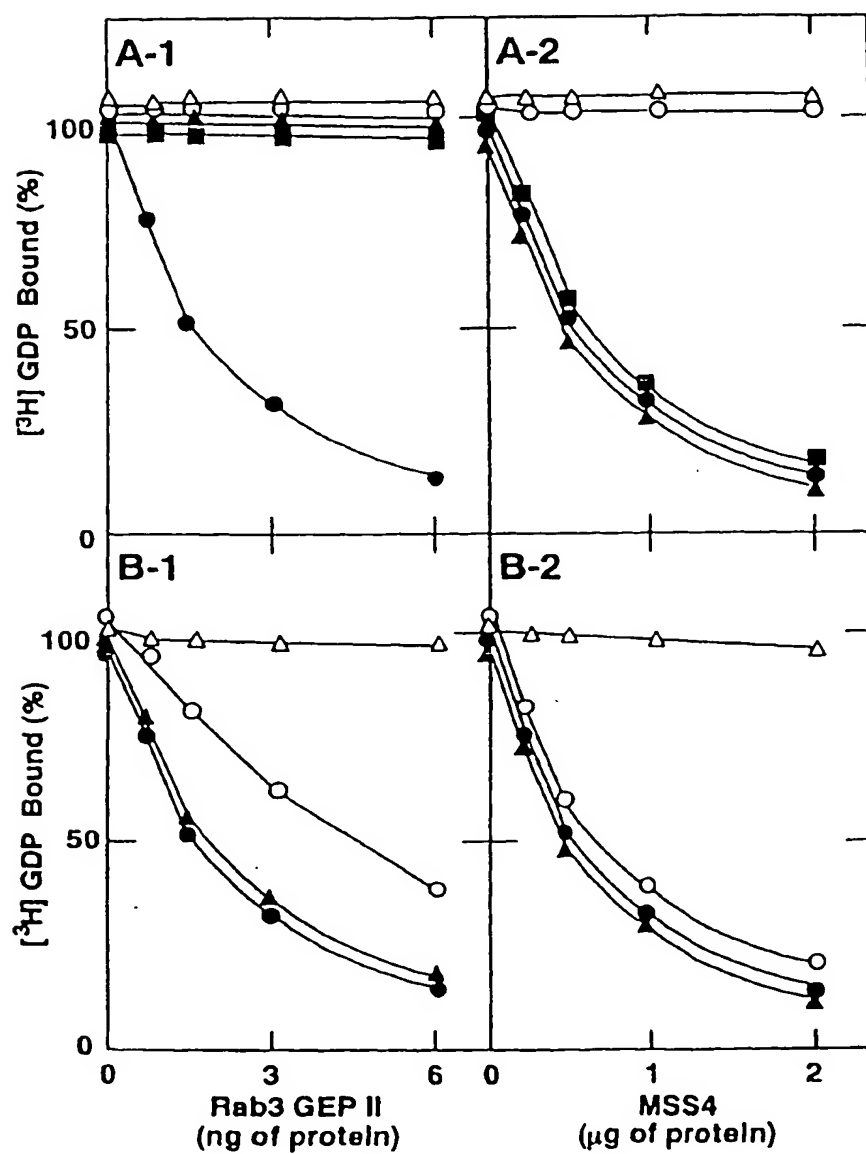
*Fig. 2*

Fig. 3

